69. The method of claim 67, wherein the primary or secondary cell is a human cell.

70. The method of claim 66, wherein the vertebrate cell is an immortalized cell.

71. The method of claim 70, wherein the immortalized cell is of mammalian origin.

72. The method of claim 70, wherein the immortalized cell is of human origin.

73. The method of claim 66, wherein the homologously recombinant cell is cultured under *in vitro* conditions which permit proliferation of the homologously recombinant cell, thereby generating a plurality of homologously recombinant cells which produce the therapeutic product.

74. The method of claim 73, wherein the therapeutic product is a protein or glycoprotein that is secreted by the plurality of homologously recombinant cells.

(C1 CONT'D)

75. The method of claim 66, wherein the exon comprises a CAP site.

76. The method of claim 75, wherein the exon further comprises the nucleotide sequence ATG.

77. The method of claim 76, wherein the exon further comprises a translatable coding sequence which is in-frame with coding sequence of the endogenous gene in the homologously recombinant cell.

78. The method of claim 77 wherein the translatable coding sequence is identical to the endogenous coding sequence in the first exon of the endogenous gene in the vertebrate cell.

79. The method of claim 77 wherein the translatable coding sequence is different from the endogenous coding sequence in the first exon of the endogenous gene in the vertebrate cell.

80. The method of claim 66, wherein the therapeutic product is a hormone.

81. The method of claim 66, wherein the therapeutic product is a cytokine.

82. The method of claim 66, wherein the therapeutic product is an enzyme.

83. The method of claim 66, wherein the therapeutic product is a clotting factor.

84. The method of claim 66, wherein the therapeutic product is selected from the group consisting of antigens, antibodies, transport proteins, receptors, regulatory proteins, structural proteins, transcription factors, and ribozymes.

85. The method of claim 66, wherein the therapeutic protein or glycoprotein is selected from the group consisting of calcitonin, insulinotropin, insulin-like growth factors, parathyroid hormone, nerve growth factor, TGF-β, tumor necrosis factor, glucagon, bone growth factor-2, bone growth factor-7, TSH- β, interleukin 1, interleukin 2, interleukin 3, interleukin 6, interleukin 11, interleukin 12, CSF-macrophage, CSF-granulocyte/macrophage, immunoglobulins, catalytic antibodies, protein kinase C, superoxide dismutase, tissue plasminogen activator, urokinase, antithrombin III, DNase, tyrosine hydroxylase, blood clotting factor V, blood clotting factor VII, blood clotting factor X, blood clotting factor XIII, apolipoprotein E, apolipoprotein A-I, globins, low density lipoprotein receptor, IL-2 receptor, IL-2 receptor antagonists, alpha-1 antitrypsin, immune response modifiers, soluble CD4, FSH β, and thrombopoietin.

86. The method of claim 66, wherein the therapeutic product is α-interferon.

(C/CONT'D)

87. The method of claim 66, wherein the therapeutic product is α-galactosidase.

88. The method of claim 66, wherein the therapeutic product is glucocerebrosidase.

89. The method of claim 66, wherein the therapeutic product is blood clotting factor VIII.

90. The method of claim 66, wherein the therapeutic product is blood clotting factor IX.

91. The method of claim 66, wherein the therapeutic product is growth hormone.

92. The method of claim 66, wherein the therapeutic product is erythropoietin.

93. The method of claim 66, wherein the therapeutic product is β-interferon.

94. The method of claim 66, wherein the therapeutic product is growth hormone.

95. The method of claim 66, wherein the therapeutic product is erythropoietin.

96. The method of claim 66, wherein the therapeutic product is insulin.

97. The method of claim 66, wherein the vertebrate cell is a mammalian fibroblast.

98. The method of claim 66, wherein the vertebrate cell is a primary or secondary cell of human fibroblast origin.

99. The method of claim 98, wherein the therapeutic product is human growth hormone (hGH).

100. The method of claim 98, wherein the therapeutic product is human erythropoietin (hEPO).

101. The method of claim 98, wherein the therapeutic product is human insulin.

102. The method of claim 77, wherein the endogenous gene in the vertebrate cell encodes a protein consisting of hEPO plus the hEPO signal peptide, and upon transfection of the vertebrate cell to produce the homologously recombinant cell, the translatable coding sequence of the exon replaces amino acid residues 1-4 of the hEPO signal peptide with amino acid residues 1-3 of the hGH signal peptide.

103. The method of claim 66, wherein the regulatory sequence comprises a constitutively active promoter.

(Cancelled)

104. The method of claim 66, wherein the exogenous regulatory sequence is a mouse metallothionein-1 promoter.

105. The method of claim 66, wherein the exogenous regulatory sequence is an actin promoter.

106. The method of claim 66, wherein the exogenous regulatory sequence is a collagen promoter.

107. The method of claim 66, wherein the homologously recombinant cell is, prior to introduction into the mammal, enclosed within a barrier device which permits passage of the therapeutic product from the interior of the barrier device to the exterior of the barrier device.

108. The method of claim 107, wherein the barrier device prevents the homologously recombinant cell from escaping the barrier device.

109. The method of claim 66, wherein

(1) the DNA construct further comprises a sequence encoding an amplifiable marker permitting selection of multiple copies of the sequence encoding the amplifiable marker, and

(2) the homologously recombinant cell of step (c) is cultured under conditions which select for cells having multiple copies of the sequence encoding the amplifiable marker, thereby coamplifying (i) the sequence encoding the amplifiable marker, (ii) the coding sequence of the endogenous gene, and (iii) the exogenous regulatory sequence.

110. The method of claim 109 wherein the amplifiable marker is selected from the group consisting of dihydrofolate reductase, adenosine deaminase, and the trifunctional enzyme carbamoyl phosphate synthase-aspartate transcarbamylase-dihydroorotase (CAD).

111. The method of claim 109, wherein the vertebrate cell is of human origin.

112. The method of claim 109 wherein the vertebrate cell is a primary or secondary cell.

113. The method of claim 109 wherein the vertebrate cell is an immortalized cell.

114. A method of providing a therapeutic product to a mammal, comprising introducing into the mammal a vertebrate cell which produces the therapeutic product, the cell being generated by an *in vitro* process comprising:

(a) providing a cell the genomic DNA of which comprises an endogenous gene;

(b) providing a DNA construct comprising:

(i) a targeting sequence;

(ii) an exogenous regulatory sequence;

(iii) an exon;

(iv) a splice-donor site;

(v) an intron; and

(vi) a splice-acceptor site; and

(c) transfecting the vertebrate cell with the DNA construct, thereby generating a homologously recombinant cell in which the exogenous regulatory sequence controls transcription of (b) (iii)-(vi) in addition to all exons of the endogenous gene to produce an RNA transcript that encodes the therapeutic product.

115. The method of claim 114, wherein the vertebrate cell is a primary or secondary cell.

116. The method of claim 115, wherein the primary or secondary cell is a mammalian cell.

117. The method of claim 115, wherein the primary or secondary cell is a human cell.

118. The method of claim 114, wherein the vertebrate cell is an immortalized cell.

119. The method of claim 118, wherein the immortalized cell is of mammalian origin.

120. The method of claim 118, wherein the immortalized cell is of human origin.

121. The method of claim 114, wherein the homologously recombinant cell is cultured under *in vitro* conditions which permit proliferation of the homologously recombinant cell, thereby generating a plurality of homologously recombinant cells which produce the therapeutic product.

122. The method of claim 121, wherein the therapeutic product is a protein or glycoprotein that is secreted by the plurality of homologously recombinant cells.

123. The method of claim 114, wherein the construct-derived exon comprises a CAP site.

124. The method of claim 123, wherein the construct-derived exon further comprises the nucleotide sequence ATG.

125. The method of claim 124, wherein the construct-derived exon further comprises a translatable coding sequence which is in-frame with coding sequence of the endogenous gene in the homologously recombinant cell.

126. The method of claim 125 wherein the translatable coding sequence is identical to the endogenous coding sequence in the first exon of the endogenous gene.

127. The method of claim 125 wherein the translatable coding sequence is different from the endogenous coding sequence in the first exon of the endogenous gene.

(Cancelled)

128. The method of claim 126, wherein the vertebrate cell is a primary or secondary cell.

129. The method of claim 128, wherein the primary or secondary cell is a mammalian cell.

130. The method of claim 128, wherein the primary or secondary cell is a human cell.

131. The method of claim 126, wherein the vertebrate cell is an immortalized cell.

132. The method of claim 131, wherein the immortalized cell is of mammalian origin.

133. The method of claim 131, wherein the immortalized cell is of human origin.

134. The method of claim 127, wherein the vertebrate cell is a primary or secondary cell.

135. The method of claim 134, wherein the primary or secondary cell is a mammalian cell.

136. The method of claim 134, wherein the primary or secondary cell is a human cell.

137. The method of claim 127, wherein the vertebrate cell is an immortalized cell.

138. The method of claim 137, wherein the immortalized cell is of mammalian origin.

139. The method of claim 137, wherein the immortalized cell is of human origin.

140. The method of claim 114, wherein the therapeutic product is a hormone.

141. The method of claim 114, wherein the therapeutic product is a cytokine.

142. The method of claim 114, wherein the therapeutic product is an enzyme.

143. The method of claim 114, wherein the therapeutic product is a clotting factor.

144. The method of claim 114, wherein the therapeutic product is selected from the group consisting of antigens, antibodies, transport proteins, receptors, regulatory proteins, structural proteins, transcription factors, and ribozymes.

145. The method of claim 114, wherein the therapeutic protein or glycoprotein is selected from the group consisting of calcitonin, insulinotropin, insulin-like growth factors, parathyroid hormone, β-interferon, nerve growth factors, TGF- β, tumor necrosis factor, glucagon, bone growth factor-2, bone growth factor-7, TSH- β, interleukin 1, interleukin 2, interleukin 3, interleukin 6, interleukin 11, interleukin 12, CSF-macrophage, CSF-granulocyte/macrophage, immunoglobulins, catalytic antibodies, protein kinase C, superoxide dismutase, tissue plasminogen activator, urokinase, antithrombin III, DNase, tyrosine hydroxylase, blood clotting factor V, blood clotting factor VII, blood clotting factor X, blood clotting factor XIII, apolipoprotein E, apolipoprotein A-I, globins, low density lipoprotein receptor, IL-2 receptor, IL-2 receptor antagonists, alpha-1 antitrypsin, immune response modifiers, soluble CD4, FSHβ, insulin, and thrombopoietin.

(C/Cont'd)

146. The method of claim 114, wherein the therapeutic product is α-interferon.

147. The method of claim 114, wherein the therapeutic product is α-galactosidase.

148. The method of claim 114, wherein the therapeutic product is glucocerebrosidase.

149. The method of claim 114, wherein the therapeutic product is blood clotting factor VIII.

150. The method of claim 114, wherein the therapeutic product is blood clotting factor IX.

151. The method of claim 114, wherein the therapeutic product is growth hormone.

152. The method of claim 114, wherein the therapeutic product is erythropoietin.

153. The method of claim 114, wherein the therapeutic product is β-interferon.

154. The method of claim 114, wherein the vertebrate cell is a mammalian fibroblast.

155. The method of claim 114, wherein the vertebrate cell is a primary or secondary cell of human fibroblast origin.

156. The method of claim 155, wherein the therapeutic product is human α-interferon.

157. The method of claim 497, wherein the therapeutic product is human β-interferon.

158. The method of claim 114, wherein the regulatory sequence comprises a constitutively active promoter.

159. The method of claim 114, wherein the regulatory sequence is a mouse metallothionein-1 promoter.

160. The method of claim 114, wherein the regulatory sequence is an actin promoter.

161. The method of claim 114, wherein the regulatory sequence is a collagen promoter.

162. The method of claim 114, wherein the homologously recombinant cell is, prior to introduction into the mammal, enclosed within a barrier device which permits passage of the therapeutic product from the interior of the barrier device to the exterior of the barrier device.

163. The method of claim 162, wherein the barrier device prevents the homologously recombinant cell from escaping the barrier device.

164. The method of claim 114, wherein
(1) the DNA construct further comprises a sequence encoding an amplifiable marker permitting selection of multiple copies of the sequence encoding the amplifiable marker, and
(2) the homologously recombinant cell of step (c) is cultured under conditions which select for cells having multiple copies of the sequence encoding the amplifiable marker, thereby coamplifying (i) the sequence encoding the amplifiable marker, (ii) coding sequence of the endogenous gene, and (iii) the exogenous regulatory sequence.

165. The method of claim 164, wherein the amplifiable marker is selected from the group consisting of dihydrofolate reductase, adenosine deaminase, and the trifunctional enzyme carbamoyl phosphate synthase-aspartate transcarbamylase-dihydroorotase (CAD).

166. The method of claim 164, wherein the vertebrate cell is of human origin.

167. The method of claim 164 wherein the vertebrate cell is a primary or secondary cell.

168. The method of claim 164 wherein the vertebrate cell is an immortalized cell.

REMARKS

Claims 66-168 are now pending in the application. No new matter is added by the above amendments.

Support for Amendments

The claims added by this amendment were examined in and cancelled from the parent case, USSN 08/406,390. General support for these claims is, as in the parent case, provided throughout the specification of the present application ('718) and in the specification of 08/243,391 ('391), which is incorporated by reference into the present application, and from which the present application claims priority.

Support for methods of providing a therapeutic product to a mammal is provided throughout the two specifications, e.g., at p. 29, line 25-p. 26, line 27 of '781. Support is also found at page 7, line 15-page 8, line 7 and page 34, line 32-page 26, line 23 of '391.

Constructs containing a targeting sequence homologous to a target site within or upstream of the endogenous gene, an exogenous regulatory sequence, an exon, and an unpaired splice-donor site (claims 66-113) are supported, e.g., at page 2, line 22-page 3, line 20, and Examples 1 and 2 of '391. Constructs containing a targeting sequence, an exogenous regulatory sequence, an exon, a splice-donor site, an intron, and a splice-acceptor site are supported, e.g., at page 3, lines 20-31, and page 97, line 13-page 99, line 13 of '391.

Specific types of genes and specific genes targeted using the invention are described, e.g., at page 22, line18-page 23, line 13 of '391. Support for claims drawn to methods involving thrombopoietin is particularly provided at page 36, line 4-page 52, line 32 of '718. Support for claims drawn to methods involving DNase I is found at page 53, line 3-page 62, line 26 of '718. Support for claims drawn to methods involving β-interferon is found at page 62, line 30-page 68, line 19 of '718. As mentioned above, all of these claims were previously examined in the parent case, and found there not to entail new matter.

CONCLUSION

The claims of the amendment are in order for examination, which action is requested. Please charge $756 to our Deposit Account No. 06-1050, referencing attorney docket no. 07236-013004, for excess claims fees necessitated by this amendment. If any additional fees are due, or any credits, kindly charge those to our deposit account, as well.

Respectfully submitted,

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